Rejection of the claims under 35 U.S.C. 112, fourth paragraph

Claim 12 has been rejected under 35 U.S.C. 112, fourth paragraph as being improperly dependent in that it fails to further limit a claim from which it depends. Claim 12 has been cancelled, thus obviating this rejection.

Rejections under 35 U.S.C., 112 second paragraph

Claims 1-12 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite. More specifically, the claims have been rejected for recitation of "determining from the presence, nature and location of any such mutation or mutations, the influence thereof on the biological function of the corresponding protein and thereby on the properties of the neoplasia."

In addition, claim 1 has been rejected for recitation of '"adequate" treatment.'

Claim 3 has been rejected for recitation of "biologically functional domain."

Claim 10 has been rejected for recitation of "processing of the cancer-related gene including sequencing."

Finally, claim 11 has been rejected for recitation of "preferably."

The claims have been amended as indicated above to address the issues presented under 35 U.S.C. 112, second paragraph and to clarify the claims. Support for the amendments to claim 1 may be found on page 7, lines 16-20 and page 8, lines 14-18 of the specification. Support for the amendments to claim 2 may be found on page 5, lines 7-8 and page 3, lines 9-19 of the specification. These amendments in no way add new matter to the specification. As such, withdrawal of the rejections is respectfully requested.

Rejections under 35 U.S.C. 112, first paragraph

Claims 1-12 have been rejected under 35 U.S.C. 112, first paragraph for lack of enablement. More specifically, the Examiner asserts that the specification is not enabled for the determination of prognosis and selection of adequate treatment of cancer based on the determination of any nature of a mutation in p53 or on the determination of any location of a mutation in p53. The Examiner asserts that the specification only enables the determination of prognosis and prediction of responsiveness to adjunctive, post-surgical therapy of breast cancer based on the determination of the combination of node status and p53 mutations and the determination of prognosis based on the conserved region in which the mutation is detected. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

The present invention is drawn to a method for prognostication of the development of neoplasia and for obtaining guidance for treatment in a patient suffering from neoplasia comprising

1) determining the DNA sequence for a gene encoding p53;

2) analyzing the DNA sequence for the presence of mutations; and

3) classifying the neoplasia based on the presence or absence of a mutation and whether or not the patient is node positive or node negative.

The Examiner bases the rejection on the assertion that the specification is only enabled for a node(-)/p53(+) patient. However, the present invention presents the full analysis of 317 tumor samples and the specification further clearly teaches prognostic determination from the other combinations of nodal and p53 status. More specifically, the specification teaches:

a) for node(-)/p53(-) patients - "today's adjuvant radiation or polychemo therapy/hormone therapy after surgical removal of the tumor does not seem to have any effect." It

would be clear to one skilled in the art that this would indicate that a treating physician should use alternative therapies.

b) for node(+)/p53(+) patients - "These patients have been found to have a very poor prognosis even when given today's adjuvant therapy. A more efficient therapy is therefore required for this subgroup, such as for example autologous bone marrow transplant." Clearly this indicates to the physician that for a patient who is both node and p53 positive therapies other than conventional adjuvant therapies should be sought.

c) for node(+)/p53(-) patients - "These patients have been found to have a better prognosis than node positive patients with p53 mutations, and today's adjuvant therapy does not seem to have any effect on survival rate of the patients." Again, this indicates to the treating physician that the prognosis is poor and he should look for therapies other than conventional adjuvant therapies.

Thus, the presently disclosed method presents an analysis for prognostic determination and guidance for therapy for any of the possible four combinations of p53 and nodal status. The Examiner appears to interpret the results as only being enabled for nodal(-),p53(+) patients because only these patients respond to adjuvant therapy. However, this rejection appears to miss the point of the invention. The present invention is not directed to a method of treating cancer but rather a method of prognostication and obtaining guidance in treatment. The present invention provides such guidance regardless of the p53 and node status. While the results of the invention show that three of the four possible combinations result in a prognosis which is not optimistic for adjuvant therapy, such a negative prognosis is still a prognosis, which provides invaluable guidance to a

treating physician who would know to look to alternative, perhaps unconventional, therapies with patients who have a poor prognosis to adjuvant therapies based on p53 and node status. As such, the present invention is clearly enabled as claimed and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. 103

1) Claims 1-8 have been rejected under 35 U.S.C. 103 as being obvious over Elledge et al., in view of Callahan and Hartmann et al.

Elledge et al. is asserted to teach the detection of mutations in p53 in neoplastic samples of breast cancer as a generally poor diagnostic or prognostic factor. Elledge et al. is further relied on for teaching that exon location of the mutation affects the prognosis. The Examiner asserts that Elledge et al. do not teach the classification of neoplasia into different diagnostic/prognostic groups based on node status and p53 status.

Callahan is relied on for teaching lymph node status as the primary parameter in prognosis of breast cancer. Callahan is also relied on for teaching additional prognostic factors would be desirable.

The Examiner asserts it would be obvious to combine an analysis of p58 based on Elledge et al. with nodal status assays of Callahan to prognostically classify neoplasia.

Applicants traverse this rejection and withdrawal thereof is respectfully requested.

Elledge et al. disclose the use of SSCP (single strand conformation polymorphism) to detect the presence of mutations in p53 node negative patients. SSCP is an indirect method of detecting mutations which utilizes fragments. However, SSCP will at best only detect 80% of all mutations. As indicated on page 97, right column, with Elledge et al., only if a sample indicates a mutation by SSCP, is the sample sequenced. Thus, following the teachings of Elledge et al. many mutations

will be missed because of the inefficiency of the SSCP. This is not a factor with the present invention, which recites sequencing the p53 gene as a necessary step. As such, the present invention provides an advantage over the methods of Elledge et al. which are in no way suggested in the prior art.

As a second point, the final paragraph of page 100 of Elledge et al. states,

> the absence of a p53 alteration does not by itself define a node negative group of patients whose risk of relapse is low enough that most physicians would consider not giving adjuvant therapy. The use of other factors in combination with p53 will be needed to achieve this goal.

It is clear from this statement that Elledge et al., in fact, teach away from the present inventive method of combining the presence or absence of p53 mutations with node classification as a suitable method of prognosis. The present invention has overcome the inherent drawbacks and weaknesses of the method of Elledge et al. which lead them to conclude that p53 and node status would not provide adequate prognostic guidance. The present invention overcomes these drawbacks by starting with sequencing of the p53 gene, thereby picking up every patient having a p53 mutation. There is no suggestion of the recited steps of the present invention in Elledge et al. or of the advantages of following these steps.

With regard to Callahan, this article was published prior to Elledge et al. As such, it is clear that those skilled in the field, including Elledge et al., would have considered the teachings of Callahan when conducting their experiments. However, Callahan is merely an editorial article of speculation, not a scientific analysis. Elledge et al. presents a scientific analysis. It is further clear that those skilled in art would conclude based on the scientific evidence of Elledge et al. that the speculations presented in Callahan were inaccurate and the state of art is reflective in Elledge et al., which in fact, teaches away from the present invention.

As such, the present invention is not *prima facie* obvious over the combined references.

Claim 9 has been rejected under 35 U.S.C. 103 as being obvious over Elledge et al., in view of Callahan and Hartmann et al. and in further view of Mitsudomi et al. Mitsudomi et al. is asserted on for mutated p53 protein may have a high sensitivity to cytotoxic therapy.

Claims 10-12 have been rejected under 35 U.S.C. 103 as being obvious over Elledge et al., in view of Callahan and Hartmann et al. and in further view of Hedrum et al. Hedrum et al. is asserted to teach the use of automated, robotic workstations in the amplification and solid phase sequencing of p53 DNA to detect mutations for prognostic information.

As indicated above, the present invention is drawn to a viable method of prognosis based on node and p53 status. The presently claimed method overcomes the disadvantages of the prior art which lead the prior art to teach away from using a combination of node and p53 status for prognostication. The present invention overcomes the disadvantages by basing the p53 analysis on sequencing of the gene, where as the prior art based the analysis on SSCP screening. There is no suggestion in any of the secondary references that sequencing should be used for p53 mutation screening and that such sequencing would result in a useful method of prognosis. As such, the present invention is not achieved by combining the references and the present invention is thereby not obvious over the prior art when considered either singularly or in combination. Withdrawal of the rejections and allowance of the claims are thereby respectfully requested.

As the above-presented amendments and remarks address and overcome the rejections of the Examiner, withdrawal of the rejections and reconsideration and allowance of the claims are respectfully requested. Should the Examiner have any questions regarding the present application, she is requested to contact MaryAnne Liotta, PhD (Reg. No. 40,069) in the Washington DC area, at (703) 205-8000.

Pursuant to 37 C.F.R. § 1.17 and 1.136(a), the Applicants respectfully petition for a two (2) month extension of time for filing a response in connection with the present application and the required fee of $400.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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